

Haemorrhagic and perivenous encephalitis : a clinical-pathological review of 38 cases

M. NOEL HART AND KENNETH M. EARLE

*From the Department of Pathology (Neuropathology),
University of Missouri Medical Center, Columbia, Missouri 65201,
and the Armed Forces Institute of Pathology, Washington, D.C. 20306, U.S.A.*

SYNOPSIS Clinical and pathological data from eight cases of acute haemorrhagic leucoencephalitis (AHL) confirm the previously documented devastating features of this disease. Data from 30 cases of perivenous encephalitis (PVE) associated with viral diseases reveal pathological changes ranging from lymphocytic cuffing of vessels to severe vasculitis similar to the vasculitis of AHL. Relatively few cases show demyelination as a prominent feature. The pathological changes are unrelated to the type of underlying disease with the exception that the pathology of 'post-rubella' encephalitis tends to be mild. Two cases of rubeola and two of mumps showed viral nodules in the cortex, raising the possibility of direct viral invasion of tissue. Allowing for species differences, these changes are analogous to the pathological features of experimental allergic encephalitis (EAE); with the various pathological changes of PVE paralleling the features of ordinary EAE, while the changes of AHL and the severe cases of PVE strongly resemble hyperacute EAE.

Acute haemorrhagic leucoencephalitis (AHL) and post-infectious perivenous encephalitis (PVE) associated with childhood mumps, measles, chickenpox, and vaccination are important diseases of the central nervous system for two reasons. First, encephalitis and PVE associated with these illnesses are numerically important. They account for over 15% of childhood cases of encephalitis reported annually in the United States (Polk, 1971). Second, PVE and AHL both closely resemble experimental allergic encephalitis (EAE), which is considered to be an excellent model for the study of presumed immunological disease of the central nervous system (Levine, 1971). Thus, if EAE is to be an experimental model of PVE and AHL, then the pathology of both these diseases should be clear. Although the pathology of AHL has been well defined in the past (Hurst, 1941; Adams *et al.*, 1949), PVE has generally been considered to be a demyelinating disease (Greenfield and Norman, 1963; Behan *et al.*, 1973), and this categorization has masked appreciation of the actual diverse micropathological findings associated with the

disease. With the exception of the treatise by Carpenter and Lampert (1972), there are no recent descriptions of the variable pathology of PVE which must be accounted for by any causal theory of AHL and PVE.

For these reasons we present the previously unreported¹ clinical and pathological features of 30 cases of PVE and eight cases of AHL from the files of the Armed Forces Institute of Pathology and the University of Missouri Medical Center.

METHODS

Necropsy cases of PVE and AHL were selected which had good clinical documentation of the primary viral disease, clinical nervous system (CNS) symptoms, and sufficient pathological material (at least five blocks from various areas) for special stains. The PVE cases included 17 cases of rubeola, four of rubella, six of mumps, two of varicella, and one post-vaccination case. Special stains for myelin, axons, and glia were used on most of the cases in which these stains had not already been performed.

¹ The histopathology of some of these cases was reviewed in preparation for Carpenter and Lampert's (1972) chapter in *Pathology of The Nervous System*.

CLINICAL FINDINGS

POST-INFECTIOUS PERIVENOUS ENCEPHALITIS The 30 cases included 26 males and four females with an age range of 3 to 34 years including four cases in the first decade of life, eight cases in the second decade, 14 cases in the third decade, and one in the fourth decade.

Time lapse from onset of rash (parotid swelling in mumps) to the onset of central nervous system symptoms varied from two to 12 days overall with an average duration of 3.7 days for the rubeola cases, 4.2 days for the rubella cases, 9.2 days for the mumps cases, six days for the two cases of varicella, and 14 days for the post-vaccinal case. In many cases the rash was subsiding at the time of the onset of CNS symptoms.

In all cases the time between onset of CNS symptoms and death ranged from less than one day to 16 days (mean 3.9 days; median, three days).

Prominent cerebral symptoms were irritability, restlessness, and drowsiness, followed rapidly by stupor and then coma. Only two patients initially demonstrated prominent localizing signs which preceded signs of altered sensorium. Nineteen patients had elevated temperatures at the time of onset of neurological symptoms or shortly afterward. Eight patients had peripheral blood leucocytosis. Twelve patients had seizures sometime during the course of their illness.

Cerebrospinal fluid (CSF) findings included a normal cell count and protein concentration in four patients and haemorrhagic (traumatic) CSF in two additional patients. Cell count was elevated (range, 9–1240 cells/mm³) in 17 patients, six having all lymphocytes or mononuclear cells and one having all neutrophils. Of the 10 cases with mixed lymphocytes and neutrophils, lymphocytes predominated in six. In two cases lymphocytes predominated in the CSF early in the course of the disease, while neutro-

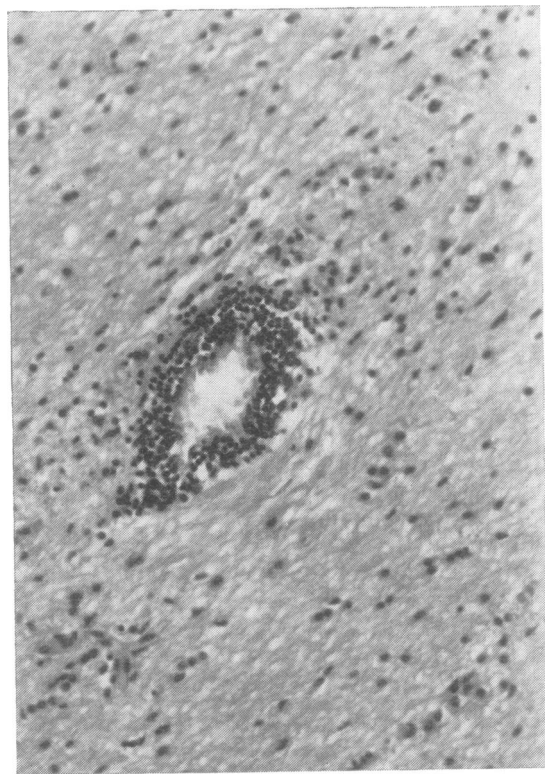


FIG. 1 *Small vessel in the white matter cuffed with lymphocytes, some of which are spreading to surrounding parenchyma. H and E, $\times 100$.*

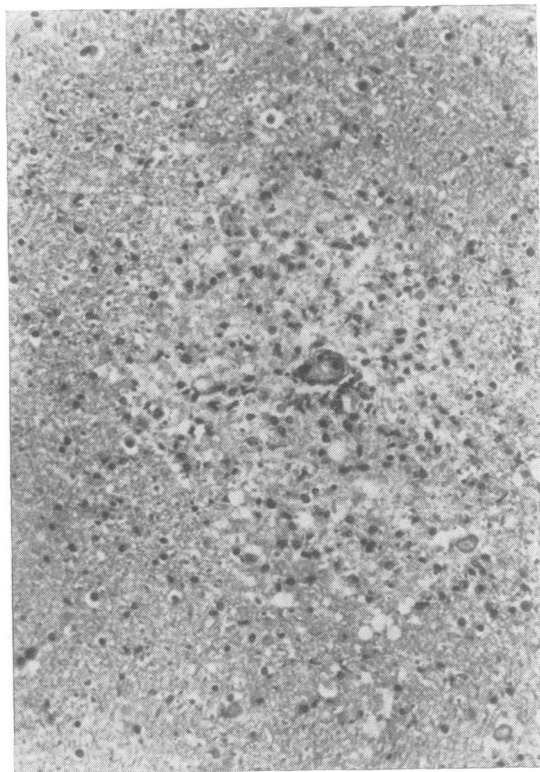


FIG. 2 *Brain-stem vessel surrounded by an extremely dense polymorphic infiltrate. H and E, $\times 100$.*

phils predominated later. Protein was listed as being elevated in only two cases and opening CSF pressure was elevated in six cases.

Viral cultures on post-mortem brain had been unsuccessfully attempted in five cases.

ACUTE HAEMORRHAGIC LEUCOENCEPHALITIS Five of patients with AHL had nonspecific upper respiratory infections from three to 12 days before the onset of neurological symptoms. The other three patients developed neurological symptoms suddenly and without warning. Six patients were male and two were female. The age range was 16 to 48 years. Time span between onset of neurological symptoms and death varied from less than 24 hours (two cases) to six days (mean 2.9 days). Seven of the eight patients experienced severe headaches as the initial symptom. The remaining patient's disease began with dizziness. All developed disorientation or a confusional state and progressed to somnolence, stupor, and coma

within hours. Additional focal neurological signs were present in three patients. Body temperature was elevated in three patients.

The CSF was examined in six patients; all had elevated cell counts ranging from 123 cells/mm³ to 1 740 cells/mm³. Neutrophils predominated in five cases and lymphocytes in one. CSF pressure was elevated in all six cases and protein was elevated in four (range 90–690 mg/dl.).

Viral studies in one case showed negative cultures from the brain but Influenza A virus was cultured from the lungs.

PATHOLOGY

POST-INFECTIOUS PERIVENOUS ENCEPHALITIS Oedema was the most conspicuous gross finding to occur in 13 of 16 cases where the gross pathology was described. Some petechial haemorrhages were present in nine cases and vessel congestion was noted in another six

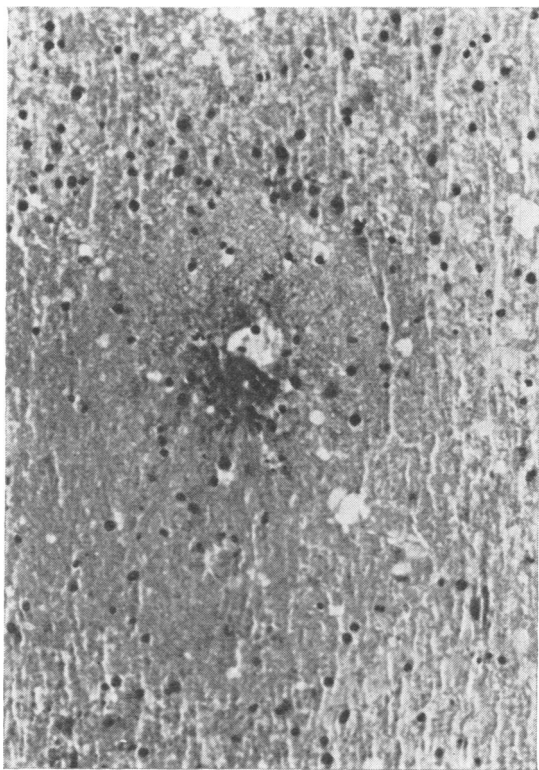


FIG. 3 Destroyed small vessel wall associated with leakage of fibrin and necrosis of surrounding tissue. Inflammation is scant in this vessel. *H and E*, $\times 100$.

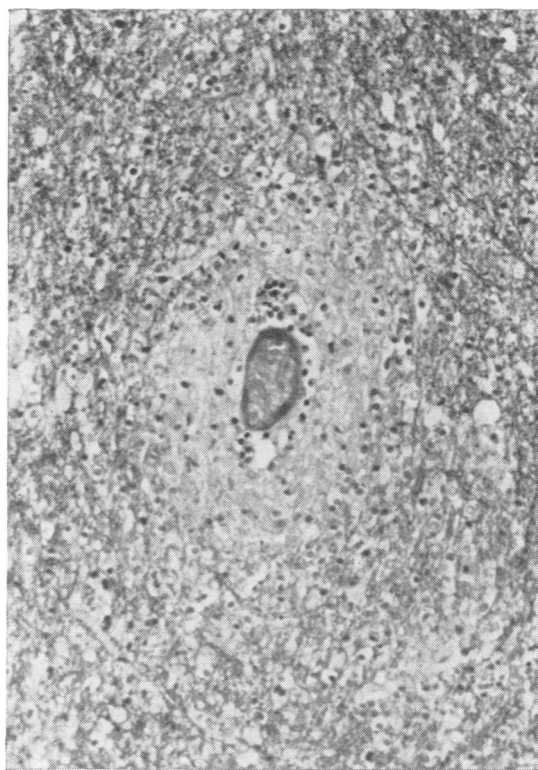


FIG. 4 Demyelinated area surrounding small vessel. A ring of fibrin-like material lines the endothelium. *Lillie*, $\times 100$.

cases on coronal sections. Petechial haemorrhages were most conspicuous in the corona radiata of the hemispheres. Closer inspection showed smaller haemorrhages in the cortical grey matter and a few in the brain-stem. This pattern was approximately the same as found in AHL. Other organ involvement varied considerably; pneumonia, severe enough to be considered as the cause of death, was present in six cases—all of rubeola.

Microscopic changes varied considerably in location, type of cellular infiltrate, and degree and category of tissue damage. One case showed only lymphocytic infiltration in the meninges without perivascular involvement of parenchyma. Technically speaking, this case should not have been included since only the meninges were involved but clinically it was a case of encephalitis after a childhood illness. Seven additional cases showed meningeal lymphocytic infiltrates in combination with parenchymal pathology. All other cases had perivascular inflam-

matory infiltrates in the following combinations: in three cases the infiltrate was predominantly limited to the Virchow-Robin space and consisted only of lymphocytes (Fig. 1). All other cases showed extension of cellular infiltration for variable distances from the vessel wall. In 10 of these cases the infiltrate consisted of lymphocytes, neutrophils, plasma cells, and microglial cells including lipid laden phagocytes (Fig. 2); in six cases the infiltrate was lymphocytes, plasma cells, and microglia. Lymphocytes alone were present in three cases and lymphocytes and neutrophils in two cases. No giant cells were seen.

Infiltrates were associated with the following tissue changes: vasculitis in seven cases, three of which showed vessel wall necrosis and fibrinous exudates associated with variable inflammatory infiltrates. The other four cases showed inflammatory cells, chiefly neutrophils, in the vessel walls without frank necrosis (Fig. 3). Twelve cases showed prominent perivascular zones of pallor; in six of these cases

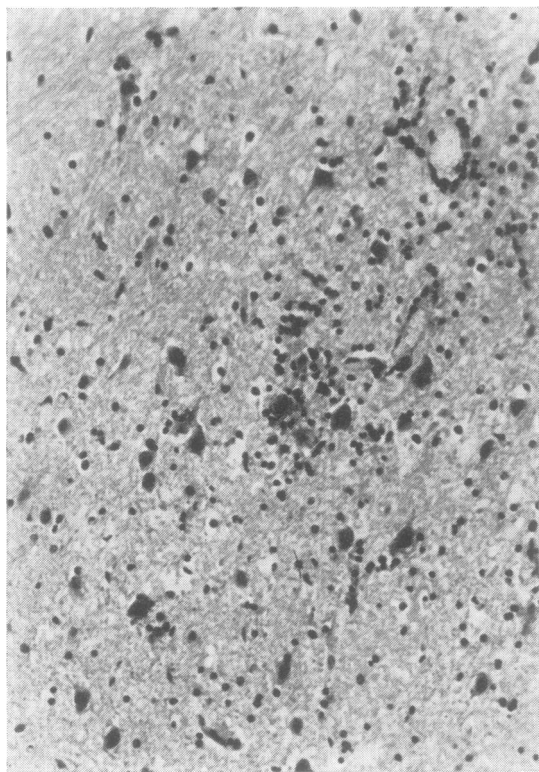


FIG. 5 Glial nodule in the cortex. *H and E*, $\times 100$.

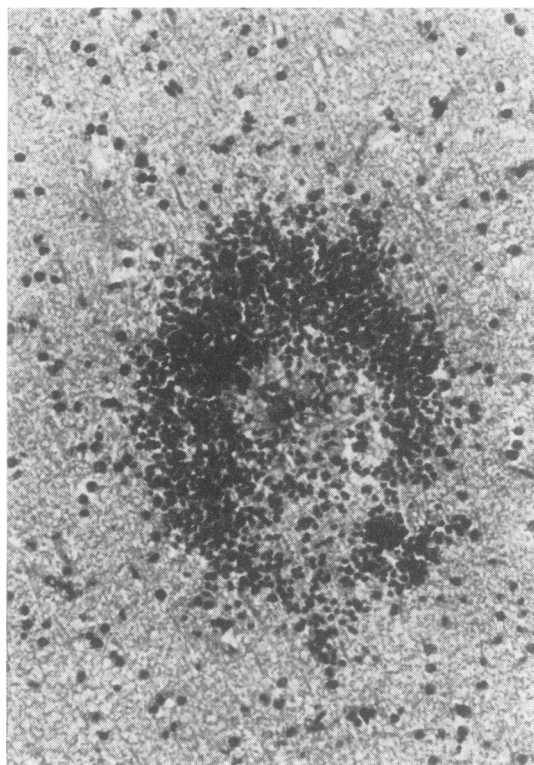


FIG. 6 Ring haemorrhage surrounding small destroyed vessel in case of acute haemorrhagic leucoencephalitis. *H and E*, $\times 100$.

the pallor consisted of frank necrosis of tissue associated with inflammatory infiltration. In the other six cases the pallor proved to be at least partial demyelination with some relative sparing of axons (Fig. 4) which was usually, but not always, associated with inflammation outside the Virchow-Robin space. Typical viral glial nodules (Babes' nodes) were present in the cortex and deep grey tissue in four cases (two mumps, two rubeola) (Fig. 5).

All of these changes were overlapping—that is, although each case showed a predominance of one type of lesion or another, the less severe types of microscopic lesions were often found. One exception to this observation was that the four cases of rubella consistently showed mild perivascular and meningeal lymphocytic infiltrates with mild, focal perivascular demyelination in two cases.

The predominant sites of involvement were as follows: supratentorial white and grey matter in equal distribution, 10 cases; white matter alone, five cases; brain-stem, five cases; cortical grey matter, two cases; deep grey matter, two cases; spinal cord, two cases; diffuse involvement, two cases. It is to be emphasized that all cases showed fairly extensive involvement.

ACUTE HAEMORRHAGIC LEUCOENCEPHALITIS Gross changes in all cases of AHL consisted of oedema and petechial haemorrhages of the corona radiata which were more marked on one side. Five of the eight cases also showed involvement of the mid-brain and brain-stem. One case involved the cerebellum to a significant degree.

Microscopically all cases showed perivascular 'ball and ring' haemorrhages around venules and arterioles. Vasculitis featuring destruction of the vessel wall with leakage of fibrin-like material was present in each case to variable degrees (Fig. 6). Inflammatory cells were present in the vessel walls and in the surrounding tissue; neutrophils were most prominent but macrophages and lymphocytes were also present. Demyelination was not present *per se* but was invariably associated with necrosis. Vascular changes were just as prominent in the grey as in the white matter but perivascular necrosis was not prominent in the grey matter. No glial nodules were seen.

General necropsy findings in two cases showed fatty changes of the liver. Perivascular microhaemorrhages associated with a neutrophilic infiltrate were present in the kidney in one case, and the spleen of an additional case showed hyperplastic germinal centres.

DISCUSSION

Acute haemorrhagic leucoencephalitis appears to be a fairly distinct pathological entity. Patients succumbing to this disease usually experience the sudden onset of severe headache with rapid progression of neurological symptoms to coma and death. The pathological picture of intense vasculitis with perivascular necrosis and haemorrhages, fibrin exudate, and neutrophilic infiltration has been well-documented previously (Hurst, 1941; Adams *et al.*, 1949). However, diagnosis is difficult in small surgical biopsy specimens because many diseases can produce similar changes in blood vessels. The focal distribution of the lesions in the white matter and the exclusion of other causes are important features of this disease.

In contrast, post-infectious perivenous encephalitis is not nearly so well defined in its pathological presentation; although all the cases of PVE have the common denominator of an underlying viral disease or vaccination, the clinical presentation and the pathological manifestations vary considerably.

The prominent histopathological features of PVE are (1) lymphocytic infiltration of meninges and perivascular spaces, (2) perivascular infiltrates which may be either single or mixed cell types, (3) conspicuous perivascular demyelination in some cases but not in others, (4) perivascular necrosis, (5) vasculitis, and (6) glial nodules of grey matter. These features are ubiquitous in their distribution and at least three of these six features are found in most cases in variable proportions. With one exception, no single microscopic finding appears to be more closely associated with one underlying disease than with the other, the one exception being the observation that the predominant pathology of the four rubella cases was lymphocytic infiltration of meninges and perivascular spaces in all four with minimal demyelination in two cases, indicating a less severe brain involvement in this disease.

In general, perivascular and meningeal lymphocytic infiltration would be compatible with either an allergic response of the brain to virus or direct invasion of the CSF by virus (aseptic meningitis).

The presence of glial nodules (Babes' nodes) is the strongest morphological evidence that there

may be an actual viral encephalitis. It is noteworthy that of the four cases showing glial nodules, two were cases of rubeola and two of mumps. Rubeola virus has been cultured from the CSF on one previous occasion (Shaffer *et al.*, 1942) and rubeola antigen has been demonstrated in the brain of a patient dying of PVE (ter Meulen *et al.*, 1973). Mumps virus is presumed directly to invade the CNS of humans (Levitt *et al.*, 1970) and is known to attack the CNS in a specific manner experimentally (Margolis *et al.*, 1974).

Demyelinated zones surrounding vessels were present to some degree in six cases while six others showed actual necrosis which was invariably associated with a polymorphic inflammatory infiltrate. Demyelination with axonal sparing was only rarely encountered in the absence of an inflammatory infiltration. Both of these lesions were often seen in the same brain. Other than the demyelination noted in the two rubella cases, the findings of necrosis and demyelination did not correlate with the type of disease pattern, or other lesions, or duration of time from onset of CNS symptoms to death. However, necrosis was more advanced in those patients who had survived the longest. Perivascular demyelination and necrosis both suggest strongly that the damaging agent emanated from the vessels. Pure demyelination might be caused by hypersensitivity to myelin basic protein but could also be caused by hypoxia, viral invasion of oligodendrocytes (Lampert *et al.*, 1973), or by any agent which was toxic to oligodendrocytes. It is noteworthy that Lisak *et al.* (1974) have recently demonstrated cell-mediated immunity to myelin basic protein in acute disseminated encephalomyelitis after non-specific viral illness. Necrosis associated with inflammatory infiltration suggests vascular release of either a toxin or a plethora of antibodies capable of reacting with numerous components of the brain parenchyma. The latter possibility would be favoured by the similarity of this finding to experimental allergic encephalomyelitis (EAE) where crude heterologous or homologous antigen is used (homogenized brain) (Ferraro and Roizin, 1954) and on the basis of temporal relationship to the initial disease. On this reasoning, we postulate that demyelination occurs primarily in those cases where the antibodies are primarily directed against myelin and that necrosis occurs when

there is production of antibodies directed against several components of the central nervous system. Also noteworthy was the presence of plasma cells in the perivascular infiltrate in ten cases, suggesting a humoral antibody component to the disease process. In EAE produced by a purified encephalitogen, humoral antibody will not cause demyelination (Seil *et al.*, 1968) but the situation may be very different in human disease where numerous antibodies may be released, some perhaps as an epiphenomenon after tissue destruction.

In the seven cases which showed vasculitis, vessel wall necrosis, and fibrin-like exudates, it is quite possible that additional antibody factors were directed against the vessel wall. The latter cases approached the pathology of AHL and three of them were microscopically indistinguishable from AHL with the exception that perivascular haemorrhages were rare. Two of these were cases of measles and one was a case of mumps. All three patients died within 24 hours of the onset of CNS symptoms. This link between AHL and PVE was first suggested by Russell (1955) who argued that the two diseases are variations of one pathological process.

Levine and Wenk (1964) and more recently Behan *et al.* (1973) have described a hyperacute form of EAE which is produced by the injection of pertussis vaccine with heterologous basic protein and complete Freund's adjuvant. Whereas the typical EAE is manifested pathologically by demyelination and perivascular cuffing of mononuclear cells, the hyperacute form shows microscopic fibrinoid necrosis of small vessel walls, neutrophilic infiltrates and exudates of fibrin strikingly similar to the typical changes both of human AHL and of these severe cases of PVE. Both hyperacute EAE and this severe form of PVE appear to differ from AHL in the paucity of perivascular haemorrhages.

Neutrophilic infiltrates in the perivascular areas were also a prominent feature of PVE in our material and generally were most prominent in the more severe cases. In addition, two cases displayed early CSF lymphocytosis followed by neutrophilia, possibly as a response to tissue necrosis. It has to be postulated that the neutrophilic exudate in the three hyperacute cases was part of the initial inflammatory response.

The geography of the microscopic lesions was

remarkable only inasmuch as it underlines that both PVE and AHL are diseases of white and grey matter and tend to be most prominent in the cerebral hemispheres. The damage surrounding vessels in the white matter is often more severe and conspicuous than in the grey matter, especially in AHL.

It is concluded that PVE is a disease of quite variable pathological presentation, irrespective of the underlying childhood type of viral disease. PVE displays a spectrum of microscopic findings ranging from minimal perivascular and meningeal lymphocytic infiltration to perivascular demyelination and necrosis, with some cases showing a severe vasculitis with pathological and clinical features identical with AHL. This is quite in keeping with the variety of tissue changes present in EAE (Ferraro and Roizin, 1954). The presence of glial nodules suggests that viral invasion of brain parenchyma may occur in some cases. On the basis of this present information and data garnered from severe EAE models, we would suggest that PVE is a hypersensitivity disease and that the pathology of PVE varies qualitatively and quantitatively with the antibody response of the host. In other words, pure lymphocytic infiltration and demyelination suggest a limited antibody response; vasculitis and parenchymal destruction imply production of heterogeneous antibodies directed against numerous tissue components of the central nervous system. In keeping with this theory is the experimental observation that EAE elicited with basic protein displays a fairly simple pathological picture predominantly consisting of perivascular lymphocytic infiltration and demyelination (Behan *et al.*, 1973), whereas EAE elicited with crude brain homogenate shows more varied microscopic pathology (Ferraro and Roizin, 1954). Glial nodules suggest that initial viral encephalitis may have unmasked tissue antigens, although this postulate is not absolutely necessary in explaining the pathophysiology of this disease. Perhaps in the hyperacute forms of PVE, and in all forms of AHL, there is a viral component, a bacterial component, or an unmasked tissue component which acts as an accelerator adjuvant as does pertussis vaccine in hyperacute EAE.

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